REMARKS

Claims 1-35 are pending in this application.

Applicants have amended claims 1 and 9 to improve their form.

Applicants have amended claim 2 to correct an inadvertent typographical error.

Applicants have amended claims 4-6 and 11-15 to replace "Seq. ID NO." with "SEQ ID NO.:".

Applicants have amended claim 8 to specify a combinatorial expression library comprising a plurality of members, wherein each member comprises a DNA sequence encoding a protein species comprising an A chain of a toxic protein in which an insert has been introduced, wherein the A chain of the toxic protein comprises a protease-sensitive loop or region and wherein the insert is a polypeptide of varying amino acid sequence having a length of at least 2 amino acid residues. Support for this amendment may be found in the specification at, *e.g.*, page 6, lines 5-8; and page 11, lines 4-9.

Applicants have amended claim 17 to specify a method for identifying a ligand that binds to a specific cell surface target/receptor, comprising the steps of (a) exposing cells to one of more members of a combinatorial protein library in accordance with claim 1; (b) selecting members of the protein library that are observed to be toxic to the cells upon cell binding or internalization; (c) evaluating the selected members of the protein library to determine the sequence of the inserted region, wherein the inserted sequence is determined by sequencing the amino acids or the nucleic acids encoding the amino acids of the inserted sequence; and (d) identifying a peptide of the sequence of the

inserted region as a possible ligand for a target/receptor on the exposed cell. Support for this amendment may be found in the specification at, *e.g.*, page 14, lines 9-11; and page 15, lines 17-20.

Applicants have added claims 24-33. Support for claim 24 may be found in the specification at, *e.g.*, page 6, lines 5-7. Support for claim 25 may be found in the specification at, *e.g.*, page 6, lines 5-7; and page 11, lines 9-10. Support for claim 26 may be found in the specification at, *e.g.*, page 6, lines 5-7; and page 11, lines 9-10. Support for claim 27 may be found in the specification at, *e.g.*, page 6, lines 5-7; and page 11, lines 9-10. Support for claim 28 may be found in the specification at, *e.g.*, page 6, lines 8-11. Support for claim 29 may be found in the specification at, *e.g.*, page 3, lines 7-11; page 6, lines 13-27; and page 8, lines 10-14. Support for claim 30 may be found in the specification at, *e.g.*, page 3, lines 2-5; page 6, line 31 to page 7, line 2; and page 7, lines 13-14. Support for claim 31 may be found in the specification at, *e.g.*, page 13, lines 10-12. Support for claim 32 may be found in the specification at, *e.g.*, in original claim 6. Support for claim 33 may be found in the specification at, *e.g.*, page 2, lines 26-29; page 5, lines 24-26; page 8, lines 16-18; page 11, lines 6-9; and page 12, line 23 to page 14, line 3. Support for claim 34 may be found in the specification at, *e.g.*, page 9, lines 8-10 and in original claim 17. Support for claim 35 may be found in the specification at, *e.g.*, page 9, lines 3-5 and in original claim 17.

None of the amendments introduces any new matter.

The Restriction Requirement

The Examiner has required restriction of the claims of this application under 35 U.S.C. § 121 into one of the following four (4) groups:

Group I: claims 1-7, drawn to a combinatorial protein library;

Group II: claim 8, drawn to a combinatorial expression library;

Group III: claims 9-16, drawn to a mutant protein; and

Group IV: claims 17-23, drawn to a method for identifying a toxic ligand.

The Examiner states that the inventions do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical features. The Examiner states that although the common technical feature is a mutant protein comprising an insert in the protease-sensitive loop of the A chain of a toxic protein, US Publication 2002/0058615 ("Wong") teaches a composition comprising bacterial-derived toxins including A chain toxins and inserting peptides into disulfide loops; and US Patent 7,314,632 ("Fitzgerald") teaches Pseudomonas exotoxin A-like chimeras wherein the disulfide loop has an insertion.

Applicants traverse the restriction of Groups I-IV and submit that the restriction is improperly drawn for the following reasons.

The present application is a national stage application submitted under 35 U.S.C. § 371 of international application PCT/CA2004/000443. PCT Rule 13 governs the unity of invention guidelines for national stage applications submitted under 35 U.S.C. § 371. To fulfill the requirements of unity of invention according to PCT Rule 13, "the [international] application shall relate to one invention only or to a group of inventions so linked as to form a ***single general inventive concept***." (Rule 13.1) (emphasis added). A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that

involves at least one common or corresponding special technical feature. The expression "special technical features" is defined as meaning those technical features that define a contribution which each claimed invention, considered as a whole, make over the prior art. *See* PCT Rule 13.2.

Applicants submit that the special technical feature shared among the group of inventions of the pending claims is a mutant protein comprising an A chain of a toxic protein comprising a protease-sensitive loop or region in which an insert has been introduced. The subject toxin proteins are known to comprise two or more polypeptide domains or subunits responsible for distinct functions, referred to as A and B. The A chain confers the cytotoxic activity of the toxin protein whereas the B chains form a binding moiety which binds the A chain of the toxin protein to a receptor on a cell surface, thereby delivering the A chain to the cell. *See* p. 6, lines 25-27 of the specification. Binding of the toxin to the cell surface is critical to the introduction into the cell and thus for toxicity. Because of this, the A chain alone is not significantly toxic. *See* p. 8, lines 6-8 of the specification. The mutant proteins of the present application are characterized by an insert of 2 or more amino acid residues introduced in the A chain of a toxin protein in order to create an artificial binding domain within the A chain. The binding specificity of these artificial binding domains within the A chain are independent of and different from the normal specificity associated with the B chain binding domain of toxic proteins.

All of the pending claims share this technical feature. The claims of Group III are directed to these mutant protein species. The claims of Group I are directed to combinatorial protein libraries comprising a plurality of these mutant protein species. The claims of Group II are directed to combinatorial expression libraries encoding these

mutant protein species. Finally, the claims of Group IV are directed to methods of using these mutant protein species (*e.g.*, for identifying a toxic ligand). Thus, the different "inventions" of Groups I-IV are linked to form a single general inventive concept because they are all characterized by the novel mutant protein species.

The Examiner agrees that the common technical feature of the pending claims is a mutant protein comprising an insert in the protease-sensitive loop of the A chain of a toxic protein (*see* Office Action, page 2). However, the Examiner contends that Wong and Fitzgerald also teach this feature. Specifically, the Examiner contends that Wong discloses a composition comprising bacterial-derived toxins including A chain toxins and inserting peptides into disulfide loops and that Fitzgerald discloses Pseudomonas exotoxin A-like chimeras wherein the disulfide loop has an insertion. Applicants traverse and disagree with the Examiner's characterization of these two documents.

Wong describes targeting peptides for tumor-derived endothelial cells, wherein the peptides may be linked to a therapeutic agent, including an A chain toxin. However, Wong does not disclose an insert introduced in a protease sensitive loop or region of the A chain of a toxic protein. Rather, Wong describes inserting a variety of short peptides within the disulfide loop of thioredoxin (*see* paragraph 32 of Wong), which is ***not*** the A chain of a toxic protein comprising a protease-sensitive loop or region. Instead, thioredoxins are proteins that act as antioxidants by facilitating the reduction of other proteins by cysteine thiol-disulfide exchange. Wong merely describes a "fusion" protein of a targeting peptide linked to a therapeutic agent such as an A chain toxin. In contrast, the mutant proteins of the present application are characterized by an insert of 2 or more amino acid residues introduced in the protease-sensitive loop or region within the

A chain of the toxin protein. Thus, Wong does not disclose or suggest the mutant proteins which characterize the special technical feature of the claimed inventions.

Fitzgerald describes Pseudomonas exotoxin A-like chimeras comprising at least a cell recognition binding domain (domain Ia) to allow binding to cell surface receptors and a translocation domain (domain II) to effect translocation of the chimeric protein. The chimeras also comprise a non-native epitope domain which serves as an immunogen to elicit an immune response against a non-native epitope, which may be inserted into the cysteine-cysteine loop region of domain IIb of Pseudomonas exotoxin A. However, Fitzgerald does not disclose an insert that is introduced in a protease sensitive loop or region of the A chain of a toxic protein. Rather, the non-native epitope domain is inserted into the domain IIb of Pseudomonas exotoxin A, which is ***not*** the A chain. As discussed above, the mutant proteins of the present application are characterized by having an insert introduced in the A chain of a toxin protein comprising a protease-sensitive loop or region in order to create an artificial binding domain within the A chain. Fitzgerald does not disclose or suggest this special technical feature. Thus, Fitzgerald does not disclose the mutant proteins of the present application.

Accordingly, applicants submit that the pending claims fulfill the requirements of unity of invention under PCT Rule 13. Specifically, the group of inventions are linked so as to form a single general inventive concept because they all relate to a mutant protein comprising an A chain of a toxic protein comprising a protease-sensitive loop or region in which an insert has been introduced. These mutant proteins, libraries comprising them, expression libraries which produce them and methods for their use define the special technical feature that the invention as a whole provides over the

prior art. For all the foregoing reasons, applicants request that the Examiner withdraw the restriction.

If the Examiner does not agree with applicants' request to withdraw the restriction, applicants provisionally elect with traverse the claims of Group I for initial substantive examination. 37 C.F.R. § 1.143. Claims 1-7 read on the elected claims. This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority here from.

Species Election

The Examiner states that the application contains claims directed to the following patentably distinct species:

> **For Group I**: a single, specific species of where the insert is introduced (*see* claims 4-6);
>
> **For Group III**: a single, specific species of where the insert is introduced (*see* claims 11-12 and 15); and
>
> **For Group IV**: a single, specific species of how the target/receptor is displayed (*see* claims 20-22).

The Examiner has required applicants to elect a single species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner further states that upon allowance of a generic

claim, applicants will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

Applicants traverse the species election because it is based on an improperly drawn restriction, for reasons discussed above. If the Examiner does not agree with applicants' request to withdraw the species election, applicants provisionally elect with traverse for initial examination the species of the insert being introduced between amino acids 242 and 261, as defined with reference to SEQ ID No.: 1 for Group I. Claims 1-4 and 7 encompass the elected species. Applicants make this species election specifically without waiver of applicants' right to seek patents on the non-elected species in this application or in applications claiming the benefit and priority of this application.

CONCLUSION

Applicants request favorable consideration of the application and early allowance of the elected claims.

Respectfully submitted,

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